enclosed electronic and paper copies of the Sequence Listing include no new matter that goes beyond the original application as filed, but are supplied as requested in the Office Action. Furthermore, the above amendments regarding the sequences, which merely direct the insertion of the Sequence Listing and insertion of sequence identifiers, include no matter that goes beyond the original application as filed. Applicants respectfully submit that the above-identified application is now in compliance with 37 C.F.R. §§ 1.821-1.825 and WIPO Standard ST. 25. Accordingly, none of these amendments constitutes new matter.

5. Applicants acknowledge with thanks that the rejection based upon 37 C.F.R. § 102(a) anticipation has been overcome.

6. Claims 14, 18, and 19 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-14 of U.S. Patent No. 4,876,194. The Action maintains the position that the protein L as set forth in the issued patent is the same, or in the alternative an obvious or analogous variant of the instantly claimed protein of SEQ ID NO:1.

Applicants respectfully traverse this rejection on the following grounds.

The present invention arises from the identification of the amino acid sequence of protein L and the identification of specific regions of protein L which provide binding to immunoglobulin light chains. The Action contends that the mere discovery that the claimed composition possesses a property not disclosed in the prior art does not alone defeat a *prima facie* case of obviousness. Applicants submit that the courts have found that what cannot be contemplated or conceived cannot be obvious. In *In re Deuel*, the court stated:

> Existence of a general method of isolating cDNA or DNA molecules is essentially **irrelevant** to the question of whether **specific molecules themselves** would have been obvious, in the absence of other prior art that suggests claimed DNAs, nor does fact that general process can be conceived in advance for preparing undefined compound mean that claimed specific compound was precisely envisioned and therefore obvious; Board of Patent Appeals and Interferences thus erred by rejecting claims for isolated and purified DNA and cDNA molecules encoding heparin-binding growth factors based upon alleged obviousness of method of making molecules, **since applied references do not teach or suggest claimed cDNA molecules**....Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious **a particular**

> **claimed cDNA.** "Obvious to try" has long been held not to constitute obviousness. (emphases added) *In re Deuel* 51 F.3d 1552, 34 U.S.P.Q. 2d1210, 1214, 1215; Fed. Cir. 1995.

Therefore, the courts have found that as the claims define **new chemical entities** in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest **the claimed compounds** to a person of ordinary skill in the art.

The present invention represents an analogous situation to *In re Deuel* in that the prior art discloses a band of 95,000 molecular weight on an SDS gel. Nowhere in the prior art is **the claimed compound** (*i.e.*, the new chemical entity set forth in SEQ ID NO:1 and the further defined functional domains thereof recited as B1 through B4) disclosed or even suggested. The skilled artisan, therefore, could not conceive or contemplate the claimed amino acid sequence of SEQ ID NO:1, or the functional domains thereof, regardless of the existence of a general method of sequencing protein or cDNA molecules. Therefore, as the courts have ruled, the claimed specific sequence of SEQ ID NO:1 and the functional binding domains thereof, would not have been obvious to the skilled artisan.

Additionally, applicants submit that the present invention arises from the identification of the specific regions of protein L which provide binding to immunoglobulin light chains. Thus, the claims recite specific polypeptides which comprise or consist essentially of the specific binding domains B1 to B4 either alone or in combination, none of which is described or even suggested in the prior art. Applicants note that the total sequence of B1 to B4 which is contained in SEQ ID NO:1 comprises about 300 amino acids. This is by no means equivalent to the complete sequence of protein L which is more than 700 amino acids long. Applicants further urge that the function of these various domains would not have been obvious to the skilled artisan given the disclosure in the cited primary citations U.S. 4,876,194 and EP 0 255 497 (which are equivalent) of a protein of apparent molecular weight of about 95,000. The prior art does not provide the skilled person with teaching which would lead to the preparation of these specific polypeptides. The primary citations provide a description of the isolation and characterization of protein L though without any sequence information. Moreover, these citations do not identify the domain structure of the protein or give any indication of any particular regions or domains which are responsible for antibody binding of the protein, as

recited in the instant claims. It might be reasonable to expect from the art that certain portions of the protein are more responsible for antibody binding than others. However, *prima facie*, there is nothing described or suggested in the prior art to lead the skilled artisan to the specific polypeptides which have been identified as responsible for binding to antibodies. The sequences of the present invention are capable of binding to all classes of immunoglobulins (IgG, IgM, IgA, IgD and IgE) and, as described in the specification, may be combined in a hybrid protein with sequences capable of combining to the heavy chain of antibodies such as the hybrid with protein G described in Example 2. Such a protein is able to bind 89% of all human antibodies since IgG is the quantitatively dominating Ig class.

In light of the above remarks, applicants urge that the prior art provides no teaching that would lead to the claimed protein or domains thereof. Applicants submit that the presently claimed invention is not obvious in view of the cited references and the Examiner may properly withdraw this ground of rejection.

6. (second No. 6) Claims 15-17 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-14 of U.S. Patent No. 4,876,194 in view of Guss et al. The Action alleges that applicants have not set forth any evidence of record to support the assertion that obtaining the sequence of the L protein and identification of particular domains that bind immunoglobulin light chain was unusually difficult.

Applicants respectfully traverse this rejection and submit that the Declaration of Dr. Sjöbring filed with the response to the Office Action of April 26, 2001, clearly sets forth evidence to support the assertion that the sequencing of protein L was unusually difficult. For example, in part 2 (i), the Declaration states that a long period elapsed between the initial description of the protein and the subsequent isolation of the sequence. In part 2 (iii) of the Declaration, Dr. Sjöbring states that cloning of larger fragments than the partial sequences described by Kastern, et al., proved unsuccessful until a different system was employed. Additionally, in part 2 (iv), Dr. Sjöbring states that the repetitive nature of the Ig-binding repeats of protein L made sequence determination difficult.

Furthermore, for the reasons discussed above in response to point 6 of the Action, the presently claimed protein comprising SEQ ID NO:1 and domains thereof would not have been obvious in view of the '194 patent regardless of the existence of any general method of

sequencing proteins or the difficulty in obtaining the sequence. As set forth above, the cited references fail to teach or suggest the sequence of SEQ ID NO:1 or domains thereof presently claimed by the applicants and therefore, as the courts have ruled, the new chemical entity set forth in SEQ ID NO:1 and the functional domains thereof recited as B1 through B4 could not have been obvious to the skilled artisan. Likewise, Guss et al. does not teach protein L. Guss et al. teaches protein G. However, Guss et al. does not explicitly teach the combination of any domain of protein G with protein L. In view of this, applicants respectfully submit that the cited references, taken either alone or in combination, cannot reasonably render obvious the presently claimed sequence and domains thereof. Reconsideration and withdrawal of the rejection are respectfully requested.

7. Claims 14, 18 and 19 stand rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over EP 0 255 497 or U.S. Patent No. 4,876,194 for the reasons stated above.

Applicants respectfully traverse the rejection and submit that applicants' arguments to the Action's positions in points 6, and second No. 6 are equally applicable in the context of this rejection under 35 U.S.C. § 103(a). Applicants urge that the pending claims are patentable over EP 0 255 497 or U.S. Patent No. 4,876,194 and respectfully request withdrawal of the rejection.

9. Claims 16, 18 and 19 remain rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Applicants respectfully traverse this rejection and submit that the specific sequences recited in claim 16 are sequences for heavy chain antibody binding peptides and are illustrated in Figure 6. References are quoted at page 7, line 23 – page 8, line 13 to papers which describe appropriate gene sequences for protein A, protein G and protein H. For protein M1 (part (iii) of claim 16) reference may be made to the sequence in Figure 7. In addition, in the case of protein G, additional guidance is provided by Example 2 which describes the preparation of a fusion protein of protein L and protein G. The complete sequence of this hybrid is contained in SEQ ID NO:3. With regard to the Action's request for clarification of the relationship between claims 16 and 17, it will be appreciated from the foregoing that SEQ ID NO:3 does not include all of (i-iv) of claim 16; it contains the C domains of protein G as defined in claim 16(i)

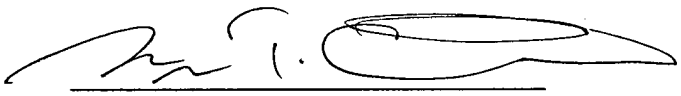
only. Thus, the references to polypeptide sequences in claims 16 and 17 are neither vague nor indefinite and would be clear to the person skilled in the art in light of the instant disclosure. Nevertheless, in order to expedite prosecution, Applicants have rewritten claim 17 in independent format as new claim 21, as per the suggestion of the Examiner during a telephone conversation conducted August 28, 2002. Applicants submit that this ground for rejection is now moot and respectfully request its withdrawal.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

Applicants respectfully submit that all of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If a teleconference would further advance the prosecution of this case, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 11, line 25 has been amended as follows:

~~The invention will now be described in more detail with reference to the accompany drawings.~~

Paragraph beginning at page 4, line 21, has been amended as follows:

Figure 1 illustrates the plasmid pHD389; the ribosomal binding sequence, the sequence for the signal peptide from **ompA** and recognition sequence for several restriction enzymes are shown (SEQ ID NO: 14);

Paragraph beginning at page 4, line 24, has been amended as follows:

Figure 2 illustrates the amino acid (SEQ ID NO:3) and nucleic acid sequence (SEQ ID NO:4) for protein LG.

Paragraph beginning at page 5, line 6, has been amended as follows:

Figure 7 illustrates the amino acid (SEQ ID NO:6) and nucleic acid sequence (SEQ ID NO: 5) for protein M1.

Paragraph beginning at page 12, line 5, has been amended as follows:

It has been found that a protein L peptide (expressed in *E. coli*) constructed of the sequence ala-val-glu-asn (SEQ ID NO:15) domain B1 (from protein L) binds to the light chains of the immunoglobulins (W. Kastern, U. Sjöbring and L. Björck. 1992. Structure of peptostreptococcal protein L and identification of a repeated immunoglobulin light chain-binding domain. J. Biol. Chem. 267 (18):12820-5). Since this simple protein L-domain has a relatively low affinity to Ig, (1×10^7 M^{-1}), and since the naturally occurring protein L which is constructed of several mutually similar domains (B1-B5) has a high affinity to Ig (1×10^{10} M^{-1}) four of these domains have been expressed together in the following way:

Paragraph beginning at page 12, line 13, has been amended as follows:

PL-N and PL-C1 are synthetic oligonucleotides (manufactured by the Biomolecular Unit at Laund University (Sweden) in accordance with applicant's instructions) which have been used to amplify a clonable gene fragment which is amplified with PCR (Polymerase Chain Reaction) and which codes for four Ig-binding protein L domains (ala-val-glu-asn-Bl-B2-B3-B4-lys-lys-val-asp-glu-lys-pro-glu-glu, SEQ ID NO:1). Amino acids in the protein L-sequence are given for the primer which corresponds to the coded strand (PL-N):

PL-N: 5′-GCTCAGGCGGCGCCGGTAGAAAATAAAGAAGAAACACCAGAAAC-3′

(SEQ ID NO:7)

valgluasnlysglugluthrproglu

(SEQ ID NO:8)

5'-end of this oligonucleotide is homologous with the coded strand in the protein L-gene (emphasized): those codons which code for the last three amino acids in the A-domain (val-glu-asn) are followed by the codons for the first six amino acids in the first of the Ig-binding domains in protein L (B1).

PL-C1: 5′-CAGCAGCA GGATTC TTATTATTCTTCTGGTTTTTCGTCAACTTT CTT-3′ (SEQ ID NO:9)

Paragraph beginning at page 18, line 13, has been amended as follows:

PL-N and PL-C2 are synthetic oligonucleotides (manufactured at the Biomolecular Unit at Lund University (Sweden) in accordance with applicant's instructions) which were used, with the aid of PCR (Polymerase Chain Reaction) to amplify a clonable gene fragment, called B1-4, which codes for four Ig-binding protein L domains (ala-val-glu-asn-B1-B2-B3-B4-lys-lys-val-asp-glu-lys-pro-glu-glu, SEQ ID NO:1):

PL-N: 5′-GCTCAGGCGGCGCCGGTAGAAAATAAAGAAGAAACACCAGAAAC-3′

(SEQ ID NO:7)

valgluasnlysglugluthrproglu

(SEQ ID NO:8)

P1-C2: 5'-CAGCAGCAGCCATGGGTTCTTCTGGTTTTTCGTCAACTTTCTTA-3',

(SEQ ID NO:10)

Paragraph beginning at page 19, line 10, has been amended as follows:

It is known that a simple C-domain from protein G will bind to IgG (B. Guss, M. Eliasson, A. Olsson, M. Uhlen, A.-K. Frej, H. Jörnvall, I. Flock and M. Lindberg. 1986. Structure of the IgG-binding regions of streptococcal protein G. EMBO. J. 5: 1567-1575). The strength at which a simple C-domain binds to IgG is relatively low (5×10^7 M^{-1}). A fragment which consists of two C-domains with an intermediate D-region having a length of 15 amino acids, however, has a considerably higher affinity to IgG (1×10^9 M^{-1}). CDC-N and CDC-C are oligonucleotides which have been used as PCR-primers to amplify a clonable DNA-fragment, designated CDC, which codes for two IgG-binding protein G-domains (pro-met-asp-CDC-met).

CDC-N: GG CCATGG ACACTTACAAATTAATCCTTAATGGT (SEQ ID NO:11)

metaspthrtyrlysleuileleuasngly (SEQ ID NO:12)

CDC-C: C AGGTCG ACTTATTACATTTCAGTTACCGTAAAGGTCTTAGT (SEQ ID NO:13)

In the Claims:

New claim 21 has been added.

Claims 14 and 15 have been amended as follows:

14. (Thrice Amended) A protein having the ability to bind to the light chains of immunoglobulins, selected from the group consisting of:

(a) a protein ~~comprising~~ consisting essentially of the amino acid sequence of SEQ ID NO:1;

(b) a protein ~~comprising~~consisting essentially of the amino acid sequence of at least one of the domains B1, B2, B3 or B4 of (a) wherein,

(i) domain B1 is comprised of from amino acid 5 to amino acid 80 of SEQ ID NO:1;

(ii) domain B2 is comprised of from amino acid 81 to amino acid 152 of SEQ ID NO:1

(iii) domain B3 is comprised of from amino acid 153 to amino acid 224 of SEQ ID NO:1

(iv) domain B4 is comprised of from amino acid 225 to amino acid 296 of SEQ ID NO:1; and

(c) a protein ~~comprising~~consisting essentially of the sequence of multiples or mixtures of the domains of B1, B2, B3 or B4 of (b).

15. (Amended) A hybrid protein ~~comprising~~ consisting essentially of one or more of the B1-B4 domains according to claim 14 which bind to the light chains in immunoglobulins of all classes, and domains which bind to heavy chains of immunoglobulin G.